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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/025,380	12/19/2001	Jiangchun Xu	210121.471C14	4505

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,380	XU ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20031110*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment and reply filed November 10, 2003 is acknowledged and has been entered. Claim 13 has been canceled.

2. Claim 12 is pending in the application and is currently under prosecution.

Grounds of Objection and Rejection Withdrawn

3. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed July 8, 2003 have been withdrawn.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Amit et al. (*Endocrinology* 1986 February; **118** (2): 835-843) in view of Berndorff et al. (*J Cell Biol* 1994 June; **125** (6): 1353-1369) and Streit et al. (*Recent Results Cancer Res* 1996; **142**: 19-50) for the reason set forth in section 12 of the Office action mailed July 8, 2003.

Applicant has traversed this ground of rejection in the Amendment and Reply filed November 10, 2003. At pages 11 and 12 of the Amendment and Reply, Applicant has argued that the combined primary and secondary references, taken for what they teach as a whole, do not teach or suggest the claimed invention, such that the claimed invention would have been obvious to the ordinarily skilled artisan at the time of filing. In particular, Applicant has argued the following:

(a) Amit et al. does not teach antibodies that bind LI-cadherin.

(b) Berndorff et al. does not teach or suggest stimulating an immune response using antibodies against LI-cadherin.

(c) Streit et al. does not expressly refer to LI-cadherin.

(d) Because Berndorff et al. discloses LI-cadherin is different from the classical cadherins, such as E-, P-, and N-cadherin, the skilled artisan would have no reason to suspect that LI-cadherin behaves as cadherins described by Streit et al.

(e) Accordingly, the skilled artisan would have had no motivation to combine the references to arrive at Applicant's invention.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Admittedly, Amit et al. does not disclose antibodies that bind LI-cadherin; Berndorff et al. does not teach or suggest stimulating an immune response using antibodies against LI-cadherin; and Streit et al. does not expressly refer to LI-cadherin. Nevertheless, in response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, although Amit et al. does not teach LI-cadherin, Berndorff et al. does. Although Berndorff et al. does not teach or suggest stimulating an immune response using antibodies against LI-cadherin, Amit et al. discloses a method, which would have been understood by the artisan of ordinary skill to provide an effective means to produce antibodies against a receptor of a particular protein of interest *without need of isolating and purifying the receptor itself*,

comprising stimulating an immune response in a warm-blooded animal comprising administering to the animal a composition comprising a physiologically acceptable carrier and an antibody that binds specifically to the receptor of the particular protein of interest. Again, Berndorff et al. teaches LI-cadherin, which Berndorff et al. discloses is a novel member of the cadherin family of cell adhesion molecules that is expressed solely in liver and intestine, and which localizes to the basolateral domain of hepatocytes and enterocytes. Streit et al. discloses members of the cadherin family of cell adhesion molecules and their receptors play an important role in cell adhesion and in particular, tumor cell migration, invasion, and metastasis. Given the facile means taught by Amit et al. to produce antibodies against a receptor of a protein of particular interest to a scientific investigator, which notably does not require the investigator to have first isolated the receptor, but only the protein of interest, and given the general importance of members of the cadherin family of cell adhesion molecules in processes such as cell adhesion, tumor cell migration, tumor cell invasion, and tumor cell metastasis, it would have been obvious to one of ordinary skill in the art, as of the filing date sought by Applicant in the instant application, to have produced antibodies against the receptor of LI-cadherin because it was understood that such antibodies are very useful reagents that can be used in a variety of ways to study and characterize the expression and function of a protein of interest, which in this case would have been LI-cadherin.

In response to Applicant's argument, Streit et al. does not expressly refer to LI-cadherin and because Berndorff et al. discloses LI-cadherin is different from the classical cadherins, such as E-, P-, and N-cadherin, the skilled artisan would have no reason to suspect that LI-cadherin behaves as the cadherins described by Streit et al., the Examiner disagrees. Although Berndorff et al. teaches LI-cadherin differs from other members of the cadherin family, Berndorff et al. teaches LI-cadherin is a member of the family and thus share structural features with other members. For example, at page 1366, in the paragraph to which Applicant has referred in their arguments, Berndorff et al. teaches the best conserved domain of LI-cadherin is the domain shown to be involved in the adhesive function and binding specificities of E- and P-cadherin.

The similarities between LI-cadherin and other members of the cadherin family support the assignment of LI-cadherin to the structurally and functionally related family. Nevertheless, despite differences between LI-cadherin and other cadherins, the disclosure of Berndorff et al. to which Applicant has referred would not have dissuaded the artisan of ordinary skill from using an antibody that binds specifically to LI-cadherin to produce an antibody that binds specifically to a receptor of LI-cadherin in a manner that is analogous to the method used by Amit et al. to produce antibodies against the prolactin receptor, particularly since one could do so *without need of isolating and purifying the receptor itself*. Steit et al. discloses the cadherins, as a class of proteins, are calcium-dependent cell-cell adhesion molecules, which even if not involved in the progression of cancer, are important determinants of tissue morphology (page 25, paragraph 2). Streit et al. further discloses, "[t]he important property of cadherins is their binding specificity, since cadherins connect cells to each other by selective binding" (page 25, paragraph 2). Accordingly, it follows that the ordinarily skilled artisan would have an interest in identifying the protein, or receptor to which LI-cadherin binds, regardless of whether or not LI-cadherin functions similarly to other cadherin types or subclasses of the larger cadherin family. Avoiding the inherent problems in isolation and purification of the receptor of a protein of interest, Amit et al. teaches their approach has been successfully used by others to produce antibodies against markedly different proteins, including the insulin receptor, the β-adrenergic receptor, and the acetylcholine receptor; see page 835, column 1. Given the disparate structural nature of the receptors to which the method produces antibodies, one of ordinary skill in the art would have had a reasonable expectation of success in using the same approach disclosed by Amit et al. and others to produce antibodies that bind specifically to LI-cadherin without the need to first identify and isolate the receptor itself. Given the general importance of members of the cadherin family of cell adhesion molecules, even though Berndorff et al. discloses LI-cadherin is different from other cadherins, and Streit et al. discloses each of the four subclasses of the cadherin family differs from the others (page 25, paragraph 2), if one were interested in LI-cadherin and its function as a cell adhesion molecule, as obviously Berndorff et al. for example is, then one would have been motivated to

produce an antibody against the receptor of LI-cadherin. It would have been readily appreciated by any ordinarily skilled artisan, as of the filing date sought by Applicant in the instant application, that such an antibody could be used in many different ways to characterize the function of LI-cadherin, just as Amit et al. discloses they used the antibody they produced against their receptor of interest. Contrary to Applicant's assertion, the fact that a newly discovered member of a family of proteins is different from previously described members of the family would not discourage the study of the novel member; rather, the Examiner contends, the recognized difference between a new member of a family and those previously described would have fueled a greater interest in the new member of the family.

In response to Applicant's remark, Steit et al. only teaches generally that adhesion molecules are expressed in certain cancers, the claims do not require the artisan to have expected LI-cadherin or its receptor to be expressed in cancer cells, or to be associated with the onset or progression of cancer. For the reasons discussed above, even if LI-cadherin were not found to be associated with cancer, the ordinarily skilled artisan would still have been motivated to produce antibodies that bind specifically to a receptor of LI-cadherin without the need to first identify and isolate the receptor itself using the methodology described by Amit et al., only using antibodies that bind specifically to LI-cadherin instead of prolactin.

Conclusion

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 11, 2004

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SUPERVISORY PATENT EXAMINER
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